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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,157	11/28/2000	Ross G. Clark	P1071P1D3	7537

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EXAMINER
ROMEO, DAVID S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,157	CLARK ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *2-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed March 27, 2002 (Paper No. 5) has been entered. Claims 1-7 are pending.

Applicant's election of group I, claims 1-7, to the extent that they are drawn to a peptide comprising the amino acid sequence of SEQ ID NO: 108, in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a peptide comprising the amino acid sequence of SEQ ID NO: 108 and a suitable carrier, does not reasonably provide enablement for a composition comprising a peptide comprising the amino acid sequence of SEQ ID NO: 108 and a pharmaceutically acceptable carrier or for the claimed compositions comprising SEQ ID NO: 108 and further comprising the additional agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass a composition comprising a peptide comprising the amino acid sequence of SEQ ID NO: 108 and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" in combination with the disclosed in vivo use implies some pharmaceutical use. Therefore, the initial enablement analysis should be based on whether there is any evidence that one skilled in art could not use the compound for any disclosed or well-established pharmaceutical use, i.e., treatment of some disease or condition in vivo, without undue experimentation.

The specification has disclosed that insulin-like growth factors (IGFs) circulate as ternary complexes in association with insulin-like growth factor binding proteins (IGFBPs) and an acid-labile subunit (ALS) (paragraph bridging pages 6-7) and that IGFBPs modulate the activity of IGFs (page 7, full paragraph 1). The invention is directed to compounds that prevent the interaction of an IGF with an IGFBP and these compounds can be used therapeutically for increasing the levels of biologically active IGF. Phage display libraries were used to generate peptides that could potentially inhibit the binding of an IGF to an IGFBP (page 101, full paragraph 1). Phage clones were tested for the ability to bind to IGFBP-1 or IGFBP-3 in the presence and absence of IGF-I and the clones that tested positive underwent an affinity maturation procedure (Specification, beginning at page 110, full paragraph 1). A BIAcore competition assay selected peptides SEQ ID NOs:1-14 that inhibited to varying degrees the interaction of IGF-I with IGFBP-3 (pages 114-116). A Biotin-BP assay selected peptides SEQ ID NOs:15 and 16, which inhibited the interaction of IGFBP-1 with IGF-I (pages 116-117). A radiolabeled IGF assay for IGFBP-3 binders showed that bp3-01-ox (SEQ ID NO: 9) and bp3-02-ox (SEQ ID NO: 8) inhibited IGF-I binding to an IGFBP-3 plate. In contrast, these peptides

did not inhibit IGF-I binding to an IGFBP-1 coated plate (page 117, last two full paragraphs). The ability of several synthetic peptides to block IGF-I binding to IGFBPs and release functional IGF-I was tested in a KIRA assay of IGF-I activity. BP15 (SEQ ID NO:10), BP1-01 (SEQ ID NO:15) and BP1-02 (SEQ ID NO:16) were actually shown to increase the availability of IGF-I in the KIRA assay. See the present specification at page 118. SEQ ID NOs: 15 and 16 are identical except for a four amino acid N-terminal extension on SEQ ID NO:16. BP15 (SEQ ID NO:10), was also shown to increase the amount of free IGF in human serum in an in vitro assay (Example 10, page 133). However, it is clear from the specification that not all of the peptides selected from the phage display library function as expected. See, for example, bp3-01-ox (SEQ ID NO: 9), which inhibited the binding of IGFBP-3 to IGF-I and IGF-II in the BIAcore assay (one of the most effective inhibitors of IGFBP-3 binding tested [page ~~155~~ 115, full paragraph 1]), but did not increase the levels of biologically active IGF in the KIRA assay (page 118, full paragraph 2). The specification only contemplates that affinity improvements and hence biological efficacy can be obtained with further manipulations of peptide phage libraries (page 114, full paragraph 1). Example 14 of the present specification teaches that bp3-107 (SEQ ID NO:108) inhibited IGFBP-3 binding to IGF-I by BIAcore™ competition and that it is expected to increase the availability of IGF-I in an in vitro cell culture assay. However, there are no working examples of increasing the bio-availability of IGF-I with the presently claimed peptide. Based on the teachings of the specification it is not predictable that peptides selected according to the procedures in the specification will increase the bio-availability of an IGF and treat some disease or condition in vivo. The claims do not require that the peptide increase the bio-availability of an IGF, and it would require an excessive amount of undue experimentation in the form of random,

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trial and error, and fundamentally unpredictable experimentation in order to make a peptide that has this activity from a peptide that does not have this activity. There is a lack of predictability in the art. Predicting structure, hence function, from primary amino acid sequence data is extremely complex and there doesn't exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. See Bowie (82, cited by Applicants) page 1306, column 1, full paragraph 1, or Ngo (u6) page 433, full paragraph 1, and page 492, full paragraph 2.

Further, it would require an excessive amount of undue experimentation in the form of random, trial and error, and fundamentally unpredictable experimentation in order to determine how to "pharmaceutically" use a peptide that does not increase the bio-availability of an IGF, and the specification lacks guidance for, and working examples of other pharmaceutical uses of the claimed peptide. The only disclosed uses for the claimed compositions further comprising the additional agents are in vivo uses, which the specification has not enabled for the reasons discussed above. Therefore the claimed compositions further comprising the additional agents are not enabled. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Conclusion

Claim 1 is allowable. Claims limited to a composition comprising the peptide of claim 1 and a suitable carrier or limited to a kit comprising the peptide of claim 1 are also allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
FEBRUARY 28, 2003